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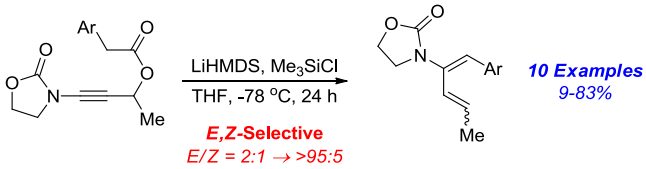

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Ireland-Claisen rearrangement of ynamides: stereocontrolled synthesis of 2-amidodienes

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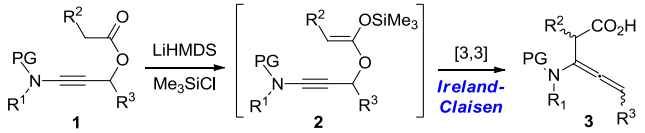
ABSTRACT

The Ireland-Claisen rearrangement of propargyl ynamido ester substrates is reported. The expected allenamide carboxylic acid products from [3,3]-sigmatropic rearrangement are not isolated, with 2-amidodienes alternatively formed in good yield with high levels of stereocontrol after decarboxylation.

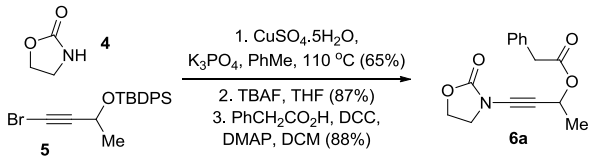
Ynamides have developed a mature and varied area of organic synthesis in recent years.[1] These compounds have been used in a raft of transition metal catalyzed reactions, such as cycloadditions and couplings.[2] Whilst a strongly electron- donating nitrogen is tempered by a nitrogen electron-withdrawing protecting group, the reactivity of ynamides is still pronounced. One area of synthetic chemistry where ynamides are arguably under-developed is in sigmatropic rearrangement chemistry. Reactions such as the Ireland-Claisen [3,3]-sigmatropic rearrangement[3] offer synthetic versatility, allowing for excellent stereocontrol and the formation of congested stereocentres.

We have recently reported the use of enamides in the Ireland-Claisen [3,3]-sigmatropic rearrangement.[4] As part of this area of research within our group,[5] we have utilized ynamides as synthetic intermediates to the requisite enamide substrates. The availability of ynamido propargyl alcohols has allowed us to ponder the possibility of conducting an Ireland-Claisen rearrangement of these ynamido propargyl systems.[6,7] If successful, this [3,3]-sigmatropic rearrangement would offer a novel stereocontrolled entry to allenamide carboxylic acid fragments (Scheme 1). As allenamides are important synthetic building blocks,[8,-10] we felt this rearrangement was worthy of investigation.



Scheme 1. Proposed Ireland-Claisen rearrangement of ynamides to allenamides.

To examine this proposal, ester **6a** was synthesized, incorporating the phenylacetate unit which had been shown to be important for the smooth rearrangement of the analogous enamide[4b] system (Scheme 2). Accordingly, bromopropargylsilyl ether **5**[11] was coupled to 2-oxazolidinone **4**, promoted by Cu-catalysis.[12] Desilylation mediated by TBAF and subsequent carbodiimide-mediated esterification formed ynamido substrate **6a** in 50% over three steps.



Scheme 2. Model Substrate Synthesis.

Initial attempts to form allenamide **3** centered upon utilizing the protocol developed for the rearrangement of enamides (Table 1).[4b] However, we were presented with a particularly complex reaction mixture, with attempted diazomethane-mediated carboxylic acid methylation observed to be non-productive,

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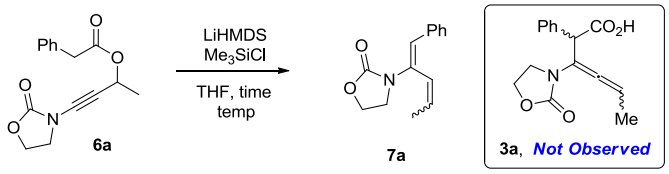
suggesting the absence of a carboxylic acid group. After careful chromatography, oxazolidinone substituted diene **7a**, with the major isomer characterized as the *Z,E*-isomer as displayed was obtained. As discussed by Hsung, there appears to be no general synthesis of aminodienes presently available to the synthesis community and therefore new methodologies that offer a controlled entry to such systems can be viewed as valuable.[13] Therefore, we sought to optimize the formation of this amidodiene product (Table 1).

Table 1. Rearrangement optimization



Entry	LiHMDS (equiv)	Me_3SiCl (equiv)	Temp (°C)	Time (h)	Yield (%)	*Z/E*
1	1.3	1.3	-78→rt	24	40	>95:5
2	1.3	1.3	-78→rt	48	41	>95:5
3	1.3	0	-78→rt	24	0	-
4[a]	1.3	1.3	-78→rt	24	13	>95:5
5	1.3[b]	1.3	-78→rt	24	25	>95:5
6	1.3	1.3	-95→rt	1.5	21	>99:5
7	1.3	1.05	-78→rt	1.5	10	>99:5
8	1.3	1.3	-40→rt	1.5	0[c]	-
9	1.3	1.3	-20→rt	1.5	0[c]	-
10	1.3	1.3	0→rt	1.5	0[c]	-
11	5.2	5.2	-95→rt	24	0	-
12	2.6	2.6	-95→rt	24	31	1:1
13	2.3	2.3	-95→rt	24	40	3:1
14	2	2	-95→rt	24	42	5:1
15	1.8	1.8	-95→rt	24	83	8:1
16	1.3	1.3	-95→rt	24	61	>95:5
17	1.05	1.05	-95→rt	24	19	6:1

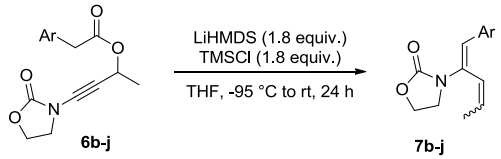
[a]Reaction conducted in PhMe. [b]NaHMDS used as base. [c]Full mass recovery of **6a**.

The rearrangement is particularly sensitive to the initial conditions employed (Table 1). For example, low loadings of base and Me_3SiCl resulted in excellent stereocontrol (entries 1-4). The reaction requires the presence of silyl chloride and therefore supports a traditional Ireland-Claisen process occurring (entry 3). The initiating temperature is crucial to any rearrangement occurring, with -95 °C offering the best results (entries 6-10). We feel it is noteworthy that **6a** is re-isolated, with full mass balance, when this reaction is initiated at -40 °C or higher (entries 8-10). Furthermore, the addition of higher loadings of base and silyl chloride is also deleterious to the final isolated yield (entries 11-17).

Previous work in our group has demonstrated that the stereocontrolled formation of aryl-substituted silylketene acetals is a more complex problem than currently is appreciated where the *E/Z* ratios are highly dependent on the loadings of base and silyl chloride, as well temperature.[14] Accordingly, we feel the presently reported rearrangement is also sensitive to the complications of forming silylketene acetals from aryl acetate esters.

This diene is presumably the result of a post-rearrangement decarboxylation. Baldwin has reported the decarboxylation of allenyl carboxylic acids, formed from the Ireland-Claisen rearrangement of propargylic esters.[15,16] However, the decarboxylation step required forcing thermal conditions (140-250 °C) to accomplish the loss of CO_2. Therefore, the presence of the *N*-substitution has a profound effect on this decarboxylation event. With an optimized rearrangement developed on phenyl acetate **6a**, we have sought to examine the scope of the arylacetate moiety (Table 2). The conditions chosen, and in particular the loading of base and silyl chloride, represents striking a balance between optimized yield and *Z/E* selectivity, as highlighted in Table 1. Accordingly, the substrate scope has been studied with 1.8 equivalents of LHMDS and Me_3SiCl.

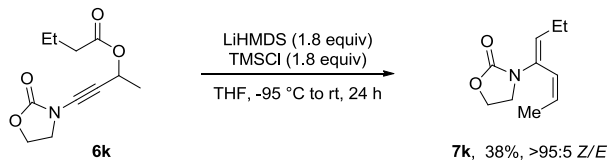
Table 2. Scope of ester functionality[17]



Entry	Ar	Diene	Yield (%)	*Z/E*
1	4-$Me_2NC_6H_4$ (**6b**)	**7b**	53	>95:5
2	4-$MeOC_6H_4$ (**6c**)	**7c**	62	9:1
3	3,4-$(OCH_2O)C_6H_3$ (**6d**)	**7d**	69	2:1
4	4-FC_6H_4 (**6e**)	**7e**	67	3:1
5	4-ClC_6H_4 (**6f**)	**7f**	65	4:1
6	4-$NO_2C_6H_4$ (**6g**)	**7g**	54	2:1
7	4-MeC_6H_4 (**6h**)	**7h**	73	3:1
8	3-MeC_6H_4 (**6i**)	**7i**	42	6:1
9	2-MeC_6H_4 (**6j**)	**7j**	43	2:1

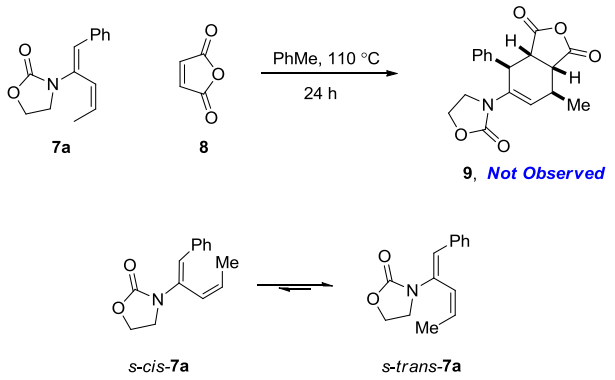
This decarboxylative rearrangement can accommodate electron-rich aryl groups (entries 1-3) and electron-poor aryl groups (entries 4-6), with reasonable yields in each instance. The aryl moiety can also cope with *ortho*, *meta* and *para*-substitution in a range of tolylacetates (entries 7-9). We would like to point out that the final *Z/E* ratio was highly sensitive to the initial conditions, as gauged by the extensive optimization of **6a**. Therefore, it may be reasonable to judge that each individual substrate may in turn have its *Z/E* selectivity improved through a local optimization process.

This decarboxylative rearrangement has been demonstrated on alkyl ester **6k** (Scheme 3). Whilst, the rearrangement in this instance is non-optimized, we feel the excellent levels of *Z/E* control are noteworthy and suggest good substrate scope in future studies.



Scheme 3. Incorporation of alkyl functionality.

Finally, we have briefly examined the feasibility of **7a** acting as a diene component in a Diels-Alder reaction (Scheme 4).[18] To assess this point, diene **7a** was refluxed in toluene for 24 hours with the reactive dienophile, maleic anhydride (**8**). Surprisingly, even though an electron-rich diene is present with an electron-deficient dienophile, no reaction was observed, with **7a** recovered with full mass balance. To account for this interesting observation, we suggest that the requisite *s-cis* conformation of **7a** cannot be accessed, even under forcing conditions, from *s-trans*-**7a.**



Scheme 4. Attempted Diels-Alder reaction and diene conformation.

In conclusion, the first Ireland-Claisen [3,3]-sigmatropic rearrangement of an ynamido ester is reported. A range of trisubstituted amidodienes has been accessed in good to excellent levels of *E/Z* selectivity and good yields. We are currently examining the synthetic utility of these amidodiene products further and investigating the observed *E/Z* stereoselectivity. Details will be reported in due course.

Acknowledgements

We acknowledge the support of University of Bath and EPSRC for studentship funding (SJH).

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17. Represenatative example; synthesis of **7b**. To a flask was added LiHMDS (1 M in THF, 0.57 mL, 0.57 mmol, 1.8 equiv.) and Me_3SiCl (73 µL, 0.57 mmol, 1.8 equiv.). The mixture was stirred at -95 °C for 0.25 h before the dropwise addition of **6b** (100 mg, 0.32 mmol, 1 equiv.) in THF (2 mL). After 0.5 h at -95 °C, the reaction mixture was allowed to warm to room temperature after which time it was stirred for an additional 24 h. The reaction was then quenched with 1:1 1 M HCl/brine solution (5 mL) and extracted with EtOAc (3 x 10 mL), with the combined organic extracts being dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification *via* flash chromatography, eluting with 2:1 petroleum ether/EtOAc, gave *Z/E*-**7b** (46 mg, 53%). FTIR (film/cm^{-1}) υ_{max}: 2903, 2798, 1741, 1604, 1519. ^{1}H NMR (500 MHz, $CDCl_3$) δH: 7.29 (2H, app. d, J = 8.5 Hz), 6.65 (2H, app. d, J = 8.5 Hz), 6.48 (1H, s), 6.17–6.08 (1H, m), 5.79 (1H, dqd, J = 11.4, 7.2, 0.8 Hz), 4.39 (1H, d, J = 7.7 Hz), 4.36 (1H, d, J = 6.7 Hz), 3.80 (1H, d, J = 6.7 Hz), 3.77 (1H, d, J = 7.7 Hz), 2.96 (6H, s), 1.66 (3H, dd, J = 7.2, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δC : 156.1, 149.5, 146.8, 130.3, 130.2, 128.5, 125.2, 123.8, 111.9, 61.6, 46.2, 40.4, 14.7; MS (ESI:+ve) *mz*: calcd. for $C_{16}H_{20}N_2O_2Na$: 295.1422, found: 295.1417, $[M + Na]^+$.
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